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| EXAMINER | |
|---|---|
| ALLEN, MARIANNE P | |

| ART UNIT | PAPER NUMBER |
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| 1647 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/570,046 | NAKAMURA ET AL. | |
| | Examiner | Art Unit | |
| | Marianne P. Allen | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *28,31-36,45 and 47-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,31-36, 45, and 47-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/5/09, 1/14/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-27, 29-30, 37-44, and 46 have been cancelled. Claims 53-54 have been newly added.

Applicant's arguments filed 10/5/09 have been fully considered but they are not persuasive.

Claims 28, 31-36, 45, and 47-54 are under consideration by the examiner.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28, 31-36, 45, and 47-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Independent claims 28, 45, 53, and 54 all recite "a method for promoting granulation formation and enhanced enclosure of a skin ulcer of a mammal." Basis is stated to be at paragraph 0136. The instant specification does not have numbered paragraphs so it is presumed applicant meant the numbering in the published application (20060199762). This paragraph is reproduced below.

*(Result-3) Promotion of enclosure (healing) of ulcer part by human recombinant HGF*

*A human recombinant HGF (10 μg/ulcer/day) was administered to a skin ulcer part for consecutive five days. As a result dose-dependent spur of enclosure (healing) of an ulcer part by the human tissue HGF was recognized from the two days after. Ten days after producing an ulcer model, in a control skin to which a physiological saline had been administered, an ulcer enclosure rate (healing rate) was 41.1±6.8%. To the contrary, an ulcer enclosure rate (healing rate) was enhanced to 85.0 ±4.0% by administration of a human recombinant HGF at 10 μg/ulcer/day. In a control (physiological saline-administered group), completion of enclosure (healing) at an ulcer part took 21 days, whereas completion of enclosure (healing) of an ulcer part was recognized on the 14th day by administration of a human recombinant HGF at 10 μg/ulcer/day (Fig. 3).*

First of all, this paragraph is with respect to a specific time and amount of administration not recited in the claims. The claims are not limited to this amount of HGF or method of administration. Secondly, this disclosure of enhanced enclosure of a skin ulcer is with respect to a saline-administered control. The claims do not recite what the enhanced enclosure of the skin ulcer is being compared to. The specification does not disclose a generic method of promoting granulation formation and enhanced enclosure of a skin ulcer of a mammal as set forth in the instant claims.

As set forth in the prior Office action, basis is not seen for the step of "providing a wound covering agent." (See claims 45 and 47-52.) The specification does not disclose manufacturing

wound covering agents nor any selection criteria for choosing a particular wound covering agent. Applicant's response does not directly address this rejection. The paragraphs pointed to disclose covering a damaged site with a wound covering material. This does not appear to be the same concept as "providing a wound covering agent." It is unclear what this step embraces and it is not disclosed in the specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 53-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 53-54 recite "HGF produced from a gene encoding a peptide." It is unclear whether this recitation is intended to mean that cells producing HGF are administered to the skin ulcer. If this type of therapy was intended, these claims would not constitute the elected invention. Applicant is reminded that gene therapy is examined in other parts of the Office. If the claims are intended to indicate that the HGF protein is recombinantly produced prior to administration to the skin ulcer, then it is unclear whether these claims differ in scope from claims 28 and 45. Because dHGF (SEQ ID NO: 1) is a mutated (not naturally occurring) protein, the only way disclosed for producing it is by recombinant production. As such, this limitation would be implicit in claims 28 and 45 and claims 53-54 would be duplicative. Finally, there is no gene for dHGF which is a mutated sequence. As such, these claims are confusing. Clarification is requested.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28, 33-36, and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toyoda et al. in view of Seki et al., Nakamura et al. (U.S. Patent No. 5,342,831), Nakamura et al. (EP 461,560 A1), and Yoshida et al. (Journal of Investigative Dermatology), and either Morishita et al. (U.S. Patent No. 7,247,620) or Morishita et al. (WO 02/089854).

Toyoda et al. discloses that overexpression of HGF in transgenic mice promotes granulation. Increased presence of HGF protein is determined by using antibodies. Toyoda discloses topical or local administration of HGF to skin wounds to promote healing and granulation formation. The reference specifically suggests using HGF to treat refractory skin ulcers from various diseases. See page 99, right column, last paragraph, as well as abstract;

pages 96-97 and 100, section 3.5, and Figures 2 and 5. Toyada et al. does not disclose the HGF of SEQ ID NO: 1.

Seki et al. discloses the HGF of SEQ ID NO: 1. This naturally occurring variant has the same biological activities as the HGF retaining the five amino acids (SEQ ID NO: 3). The variant still binds antibodies to HGF. See at least abstract and pages 323 and 325-326.

Nakamura et al. (U.S. Patent No. 5,342,831) discloses using HGF to treat skin ulcers (dermoulcers). Methods of administration, formulations, and dosages are disclosed. Gels, lotions, ointments, and aqueous solutions are disclosed. See at least column 2, lines 50-68, and column 5, lines 50-63.

Nakamura et al. (EP 461,560 A1) discloses the HGF of SEQ ID NO: 1. This naturally occurring variant has the same biological activities as the HGF retaining the five amino acids (SEQ ID NO: 3). See at least column 20, claims, and Figure 15.

Yoshida et al. discloses that inhibiting the action of HGF protein by using antibodies can suppress or inhibit granulation tissue formation. See at least abstract.

Morishita et al. (U.S. Patent No. 7,247,620) discloses treating diabetic skin ulcers by topical administration of the HGF gene to promote granulation. There is increased presence of HGF protein in the healing wound. (See at least abstract, claims, and column 3, lines 5-20; columns, 9-10, particularly column 10, lines 1-5 and 41-45; and columns 17-18.) Morishita et al. (WO 02/089,854) is the PCT from which the '620 patent originated and has an equivalent disclosure.

It would have been obvious to substitute the HGF variant of SEQ ID NO: 1 as taught by Seki et al. and Nakamura et al. (EP 461,560 A1) to treat diabetic skin ulcers as suggested by

Moroshita et al., Nakamura et al. (U.S. Patent NO. 5,342,831) and Toyoda et al. With respect to Toyada et al., one of ordinary skill in the art would have appreciated that refractory ulcers include diabetic skin ulcers. This would have been a known complication of diabetes. Morishita et al. specifically disclose treating diabetic skin ulcers. One would have been motivated to do so as Toyoda et al. and Moroshita et al. both disclose that HGF protein promotes granulation and Yoshida et al. discloses that inhibiting the action of HGF protein by using antibodies can suppress or inhibit granulation tissue formation. Based on the teachings of Nakamura et al. ('560) and Seki et al., one of ordinary skill in the art would have expected the HGF variant of SEQ ID NO: 1 to have this biological activity.

With respect to Morishita et al. (U.S. Patent No. 7,247,620), applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

With respect to enhanced wound enclosure, the specification and claim do not clearly define what this limitation requires and it is interpreted as enhancing healing. This is taught by the prior art.

Applicant's arguments focus on unexpected results. The claims do not require unexpected results and the specification asserts no unexpected results. The specification does not disclose improved solubility, heparin binding, and/or degree of mitogenic activity level as a requirement, a problem to be solved, a goal, or an unexpected result. The claims do not require this either. Any mitogenic activity resulting from the dHGF (SEQ ID NO: 1) would have been

expected to promote granulation formation and enhanced enclosure of a skin ulcer of a mammal by comparison to no treatment. Applicant has provided no experimental evidence of granulation formation and enhanced enclosure of a skin ulcer by comparison to intact HGF that does not contain the five amino acid deletion of SEQ ID NO: 1 in support of their assertion of unexpected results.

The prior art establishes that dHGF (SEQ ID NO: 1) binds to the receptor and causes signaling through the receptor, resulting in a biological effect comparable to the intact HGF. As stated in the prior Office action, Shima et al. (1994) demonstrates that dHGF was mitogenic. See Figures 1 and 2. Applicant argues that it is less potent than full length. However, one of ordinary skill in the art would still have expected it to work and result in granulation formation and enhanced enclosure of a skin ulcer. Note also that pages 29-32 of the specification indicates that the HGF can be formulated in known and conventional ways. In particular, page 32 indicates that using solubilizing agents for topical formulations is conventional. One of ordinary skill in the art would have been able to formulate dHGF (SEQ ID NO: 1) in the manner recited in the claims even if increased solubility was desired based on the knowledge in the prior art.

Claims 28, 31, 35-36, 45, 47, and 53-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toyoda et al. in view of Seki et al., Nakamura et al. (U.S. Patent No. 5,342,831), Nakamura et al. (EP 461,560 A1), and Yoshida et al. (Journal of Investigative Dermatology), and either Morishita et al. (U.S. Patent No. 7,247,620) or Morishita et al. (WO 02/089854) and further in view of De Busk et al. (U.S. Patent Publication 2004/0001878).

Toyoda et al., Seki et al., Nakamura et al. (U.S. Patent No. 5,342,831), Nakamura et al. (EP 461,560 A1), Yoshida et al. (Journal of Investigative Dermatology), Morishita et al. (U.S. Patent No. 7,247,620), and Morishita et al.are applied as above. They do not disclose the inclusion of an antiseptic in claims 31 and 47 nor the wound covering agents recited in claim 45 and 54.

De Busk et al. discloses using hydrocolloid dressings to treat skin ulcers and promote granulation formation. Antiseptics can be included with the treatment drug. Gels and liquids are disclosed for administration. See at least abstract, claims, and paragraphs [040, 045, 078].

It would have been obvious to use a wound covering agent such as those taught by DeBusk et al. with dHGF to treat a skin ulcer as suggested by the prior art as set forth above. Wound covering agents would have been routinely used to treat skin ulcers and the cited prior art suggests using dHGF for this purpose.

This rejection is maintained for reasons of record and in view of the arguments set forth above. Applicant's arguments focus on unexpected results. The claims do not require unexpected results and the specification asserts no unexpected results. The specification does not disclose improved solubility as requirement, a goal, or an unexpected result. The claims do not require this either.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is (571)272-0712. The examiner can normally be reached on Monday-Friday, 5:30 am - 2:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

mpa